the clinical biochemical laboratory do not establish a causal relation. I realise that this is a retrospective study, but a bedside observation that these patients were dehydrated and malnourished might have been more useful in management than ascribing this to a new syndrome.

A RICHARDSON

Hendon, London NW4

1 Schrier RW. Treatment of hyponatraemia. *N Engl J Med* 1985;**312**:1121-3.
2 Flear CT, Gill GV. Hyponatraemia: mechanisms and management. *Lancet* 1981;ii:26-31.
3 Ganong WF. *Review of medical physiology*. 10th ed. Los Altos, California: Lange Medical Publications, 1981:494-506.

Antisecretory drugs and gastric cancer

SIR,—Let us get to the point. Omeprazole (Drs M J Daly and A Pottage, 28 September, p 900), designed specifically to act solely on the acid secreting cells of the stomach, has selectively produced gastric neoplasms in rats. It seems highly unlikely that such specific association is either accident or coincidence. Throughout the world drug regulatory authorities demand toxicological tests to detect precisely this type of reaction in animals. Of course, if a drug produces cancer in animals it may not do so in man because there may be differences between the species in sensitivity and in the type of reactions to carcinogenic drugs. Unfortunately, we have no way of predicting human reactions.

Drug regulatory authorities, pharmaceutical companies, and certainly clinicians assume that if a drug produces no reaction in animals then at least all has been done to limit the danger to patients in so far as this is prospectively possible. On the other hand, if a drug is tainted, then—as Drs Daly and Pottage point out with regard to loxtidine—it is responsible to discard the drug, provided that there are no overwhelming benefits to compensate for the obviously possible risk. At least six drugs, other than omeprazole, which have also been specifically designed to act only on the stomach have also selectively produced gastric cancer in animals. All have been responsibly withdrawn by the pharmaceutical companies concerned because, like omeprazole, the only proved clinical benefit of this type of "potent" drug involves the treatment of the Zollinger-Ellison syndrome, which is usually aetiologically neoplastic in any case.

To summarise then, the obligatory toxicological tests have revealed what, in my opinion, is an ominous reaction to the drug. We have a choice—whether to consider the neoplastic reaction irrelevant and use the drug for treating diseases like benign peptic ulcers (which can be treated quite satisfactorily and safely by other means), or to use the drug only under exceptional circumstances, when any potential risk is outweighed by the benefit to an already compromised patient. The former course—to use omeprazole for treating benign chronic disease—seems unacceptable because it negates the very basis of toxicological testing, with all that such decision implies in moral and legal terms. I could not justify giving omeprazole to my patients.

K G WORMSLEY

Ninewells Hospital,
Dundee DD1 9SY

SIR,—Dr M J Daly and Dr A Pottage (28 September, p 900) disagree that achlorhydria is the cause of the carcinoid tumours induced in the fundus of the rat stomach by loxtidine or omeprazole and with our equation of the tumour inducing effects of these drugs (7 September, p 675). They claim that the clinical use of omeprazole in duodenal ulcer is justifiable because the tumour inducing effects of omeprazole and loxtidine are different and because omeprazole heals duodenal ulcers faster than ranitidine.

Prolonged drug induced achlorhydria can cause generalised hyperplasia and formation of carcinoids in the fundus of the rat or mouse stomach. Loxtidine causes carcinoids in both species but generalised hyperplasia in the mouse alone. Omeprazole is reported to cause hyperplasia in both species and carcinoids in the rat only.[1] The result in the mouse is, however, inconclusive for this drug because the test lasted only 18 months and occurrence of carcinoids would not be expected within this period—for example, the first carcinoid found in mice treated with loxtidine occurred in an animal that died after 591 days of treatment. Clearly, longer treatment with omeprazole may induce carcinoids in the mouse, and thus the claim that omeprazole and loxtidine differ fundamentally in their carcinoid inducing actions is at best uproved.

The mechanism of carcinoid induction in achlorhydric animals is unknown, but we are not alone in thinking that it is unlikely to result solely from hypergastrinaemia. Thus, according to Willis, "The causation of a tumour involves more than the mere persistence of hyperplasia-evoking stimuli."[2] Also, more recently, a comprehensive review stated, "Clearly, hypergastrinaemia is not the only, perhaps not even the most important factor behind the pathogenesis of ECLoma."[3] Indeed, it is easy to imagine that the critical genetic change in cells destined to become malignant, which may result from abnormal bacterial or viral growth in the stomach, might occur after brief achlorhydria and be expressed only when the immune system becomes defective.

Omeprazole can heal duodenal ulcers faster than ranitidine but only at dosages that cause greater inhibition of acid secretion than the standard daily dose of ranitidine. If rapid healing of ulcers is important it would be better achieved by increasing the dose of ranitidine, high doses of which are well tolerated,[4] than by using a drug that causes malignant tumours.

Drs Daly and Pottage's final suggestion that the long term safety of omeprazole in man should be determined by extended clinical use is worrying because, whatever else, that is not a failsafe approach to the problem. If short term achlorhydria proves to induce tumours in susceptible subjects the outcome will be very serious not only for the patients and their doctors but for the future of drug research itself.

D JACK
D POYNTER
R N SMITH

Glaxo Group Research Ltd,
Greenford

1 Ekman L, Hansson E, Havu N, Carlsson E, Lundberg C. Toxicological studies on omeprazole. *Scand J Gastroenterol* 1985;**20** (Suppl 108):53-69.
2 Willis RA. *Pathology of tumours*. 3rd ed. London: Butterworths, 1960:125.
3 Hakanson R, Ekelund M, Sundler F. Activation and proliferation of gastric endocrine cells. In: Falkmer S, Hakanson R, Sundler F, eds. *Evolution and tumour pathology of the neuroendocrine system*. Amsterdam: Elsevier, 1984:371-98.
4 Jensen RT, Collen MJ, Pandol SJ, *et al*. Cimetidine-induced impotence and breast changes in patients with gastric hypersecretory states. *N Engl J Med* 1983;**308**:883-7.

Phaeochromocytoma presenting as an acute abdomen

SIR,—The diagnosis and management of phaeochromocytoma continue to intrigue and perplex. The lesson of the week by Mr David J Jones and Ms Patricia Durning (2 November, p 1267) holds several important lessons in addition to those discussed.

Their first patient presented "profoundly shocked," and laparotomy was performed because "massive intra-abdominal haemorrhage" was suspected. A sinus tachycardia of 160 beats/min and blood pressure of 160/110 mm Hg are not consistent with "shock" in the medical rather than the lay sense. Differentiation of severe vasoconstriction from shock could have led to the early recognition of the possibility of phaeochromocytoma, a diagnosis that would have been supported by the preoperative investigations undertaken. Postoperatively vasoconstriction was not relieved by the infusion of nitroprusside, and the patient "died in acute left ventricular failure before the response to α and β blockers could be tested." α Blockade is the priority in such a patient. Intravenous phentolamine acts rapidly. If there is no response to the first dose more has to be given until the severe vasoconstriction is reversed. The systemic vasoconstriction produces a large fluid shift from the systemic circulation to the more compliant pulmonary circulation resulting in pulmonary oedema, a similar mechanism to that seen in neurogenic pulmonary oedema. If the fluid shift is reversed by adequate α blockade the pulmonary oedema will resolve. Death in this case may thus have been due to pulmonary oedema rather than acute left ventricular failure.

The second patient remained hypotensive after operation and died four hours later despite "blood transfusion and dopamine infusion." Prolonged exposure to high circulating concentrations of catecholamines causes both down regulation of receptor sensitivity and reduced extracellular fluid volume. Hypotension after removal of the tumour is treated by re-expansion of this fluid volume, and many litres of fluid may be required. Attempts to restore the blood pressure by infusing catecholamines or dopamine are unlikely to be effective as, firstly, the receptors are resistant to stimulation and, secondly, the infusion does not treat the basic problem of fluid depletion. In the non-urgent case re-expansion and α blockade takes place over several days before operation and severe hypotension is less commonly encountered at the time of operation.

The fluid depletion is the basis of a useful clinical sign which can help in diagnosing phaeochromocytoma; postural hypotension is often present.

Mr Jones and Ms Durning met these two cases as emergencies. Armchair analysis is much easier. Our points are raised not to criticise their paper but to help others who might meet similar problems.

D W BULLIMORE
K J A MILOSZEWSKI

Department of Medicine,
St James's Hospital,
Leeds LS9 7TF

Medical problems of sport diving

SIR,—One aspect of the problems of sport diving that Dr James D M Douglas (2 November, p 1224) does not mention is that of a flight in a commercial aeroplane made too soon after a scuba dive.

Owing to the reduced cabin pressure within a commercial airliner of between 5000 and 8000 feet scuba divers who fly within 24 hours of a dive may well experience symptoms of the "bends" despite having been asymptomatic at sea level; this condition poses serious logistical problems for the flight crew.

A television commercial some years ago showing a man so loth to finish his holiday that he boarded the aircraft still wearing his dripping wetsuit was, I understand, withdrawn after representations from